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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,150	02/17/2004	David Munn	NEWL-005/02US 142996-2008	1273
58349	7590	11/29/2010	EXAMINER	
COOLEY LLP				
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			1628	
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			11/29/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/780,150

Applicant(s)

MUNN ET AL.

Examiner

TIMOTHY P. THOMAS

Art Unit

1628

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 October 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 2, 5-7, 10, 17, 18, 20-24, 26, 27, 43, 97, 99-103, 105, 106, 134 and 135 is/are pending in the application.
- 4a) Of the above claim(s) 1, 5-7, 10, 17, 18, 20-24, 26, 27, 43, 97 and 102 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2, 99-101, 103, 105, 106, 134 and 135 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-946)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Response to Amendment

1. The declaration by William Paul Malachowski under 37 CFR 1.132 filed 10/28/2010 is insufficient to overcome the rejection of claims 2, 99-101, 103, 105-106 and 134-135 are rejected under 35 U.S.C. 103(a) based upon Van Den Eynde et al. (WO 00/66764; 2000; cited in a prior Office Action); in view of Peterson et al. ("Evaluation of Functionalized-Tryptophan Derivatives and Related Compounds as Competitive Inhibitors of Indoleamine 2,3-Dioxygenase"; 1994; Med. Chem. Res.; 3:531-544; IDS 5/3/2007 reference); and Karrer "Organic Chemistry" 1947; 3rd Ed., Elsevier Publishing Company, Inc., New York, pp. 94-105) as set forth in the last Office action because:

The declaration indicates that according to Peterson, the L-isomer is over six-times more effective at inhibiting the indoleamine-2,3-dioxygenase enzyme, based on Table 1. This point is not disputed with respect to IDO inhibition. However, it is noted that the D-isomer is still reported as active in the IDO inhibition assay. The declaration further states that as one of ordinary skill in the art working in the field of synthesis and testing of inhibitors of indoleamine-2,3-dioxygenase for therapeutic use, that Dr. Malachowski would not have been motivated to use the less active D-isomer of 1-methyl-tryptophan; that he would not have expected, based on Peterson, that the less active D-isomer would be a superior therapeutic composition compared to the L-isomer. This is taken to be an argument that the D-isomer is a non-proffered embodiment. MPEP 2123 (I) indicates that a reference may be relied upon for all that it would have

reasonably suggested to one having ordinary skill in the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989). MPEP 2123 (II) indicates disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use". *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). In the instant case, the D isomer is active, rendering it obvious to utilize the D isomer in place of the racemic mixture in the method taught by Van Den Eynde.

Response to Arguments

2. Applicants' arguments, filed 10/28/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

3. Applicant's arguments, see p. 7, filed 10/28/2010, with respect to the scope of enablement rejection have been fully considered and are persuasive. The rejection of claims 2, 99-101, 103, 105-106 and 135 has been withdrawn.

The claim amendment limiting the independent claims 2, 134 and 135 to require an indoleamine-2,3-dioxygenase-expressing tumor, when taken together with the species election for melanoma, is effective to overcome the rejection basis, when melanoma

that expresses IDO is under examination. Since the teachings of Van Den Eynde predict treating a subject that has a melanoma expressing IDO with D-methyl-tryptophan will have a reasonable expectation for delaying the progression of the melanoma, the subject matter under examination is considered enabled and predicted. Therefore, the rejection basis is withdrawn.

4. Applicant's arguments with respect to the obviousness rejection have been fully considered but they are not persuasive:

Claims 2, 99-101, 103, 105-106 and 134-135 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Van Den Eynde et al. (WO 00/66764; 2000; cited in prior Office Action); in view of Peterson et al. ("Evaluation of Functionalized-Tryptophan Derivatives and Related Compounds as Competitive Inhibitors of Indoleamine 2,3-Dioxygenase"; 1994; Med. Chem. Res.; 3:531-544; Ids 5/3/2007 reference); and Karrer "Organic Chemistry" 1947; 3rd Ed., Elsevier Publishing Company, Inc., New York, pp. 94-105).

The rejection is maintained for the reasons of record.

Applicant argues with respect to the scope and contents, nowhere does the cited art teach or suggest using the D isomer of 1-methyl-tryptophan for the subject to delay the progression of a tumor, or any other disease or condition for that matter. The record indicates Van Den Eynde does not teach administration of a composition that consists of only 1-methyl-D-tryptophan; i.e., all of the compositions taught by Van Den Eynde contain the racemic D/L mixture. However, it is known in the art that racemic mixtures consist of two individual stereoisomers; the isolation of the D-isomer is known in the art

(taught by Peterson); it is known in general that one stereoisomer is generally more active than another, although prediction of which one will be more active is not always known; and it is known that both isomers are active in an inhibition of IDO assay, the L-isomer more active than the D-isomer, in the particular assay reported in the art. When the component teachings are put together, it renders obvious the treatment of a subject that has an IDO-expressing melanoma with the D isomer of 1-methyl tryptophan.

MPEP 2141 indicates:

“A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton.” *KSR*, 550 U.S. at ___, 82 USPQ2d at 1397. “[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle.” *Id.* Office personnel may also take into account “the inferences and creative steps that a person of ordinary skill in the art would employ.” *Id.* At ___, 82 USPQ2d at 1396.

See also MPEP 2141.03(I).

Applicant further argues the differences between the prior art teaching of using the racemate and independently that the D and L isomers can be resolved is substantially different than the claims at issue which involve the in vivo delaying of the progression of a tumor. In vivo delaying of the progression of an IDO-expressing melanoma tumor by the racemic D/L mixture of 1-methyl tryptophan. The prior art has a clear recognition that each of the D and L isomers is separately active in an IDO-inhibiting assay, the same mechanistic basis for which the teaching of the delay of melanoma progression is taught by Van Den Eynde. One of skill in the art would have

immediately recognized from Van Den Eynde that one or both of the stereoisomers present in the racemic mixture would have been responsible for the reported anti-melanoma activity. Utilizing the D-isomer in place of the racemic mixture would have been obvious, based on the fact that IDO is inhibited by this compound and it is known that one stereoisomer is generally more active than another in living cells/subjects.

Applicant further argues that Peterson reports merely testing the ability to inhibit purified intestinal IDO enzymatic activity in vitro, and that the D isomer is significantly less potent than the L isomer; and that the level of skill in the unpredictable pharmaceutical arts is high. These points are not disputed. It is noted that Peterson also teaches methods to isolate each individual stereoisomer.

Applicant further argues that the objective indicia of non-obviousness weigh heavily in favor of non-obviousness; that Peterson teaches away from using the D isomer of 1-methyl-tryptophan for pharmaceutical uses involving inhibition. This is not persuasive, and is inconsistent with MPEP. Applicant further argues that it is unexpected that the D isomer has more potent antitumor activity in vivo; that based on the Malachowski declaration one of skill in the art would have been motivated to use the more potent L isomer and not the D isomer for IDO inhibition based on the teaching of Peterson.

There are two separate arguments that are intertwined by applicant, one for teaching away and one for an unexpected result. With respect to the teaching away, this point was addressed above: MPEP 2123 (I) indicates that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in

the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989). MPEP 2123 (II) indicates disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use". *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). In the instant case, the D isomer is active, rendering it obvious to utilize the D isomer in place of the racemic mixture in the method taught by Van Den Eynde.

With respect to the unexpected result, it might be generally assumed that the higher active L isomer would be expected to be more active as an anticancer agent, based on the mechanism of IDO inhibition taught by Van Den Eynde taken with the specific assay taught by Peterson. However, one of skill in the art would only expect this to be the case if the enzyme being inhibited is the same in the Peterson assay as the enzyme expressed in the cancer cell lines of Van Den Eynde. In fact, applicant's disclosure shows the assay is not the same (see instant Figure 10, which gives the opposite result from the Peterson assay). This does not really establish that the relative activities of the two stereoisomers of Peterson would be the same when the stereoisomers are applied to melanoma therapy. More likely to be applicable is the general teaching of Karrer, i.e., that it is expected that one isomer will be more active than another, which is not really predictable before the experiment is carried out. In

other words, the teaching of Peterson is effective to establish that both stereoisomers are active as IDO inhibitors, and when taken with the fact that the racemic mixture is known to be effective for delaying the progression of melanoma, leads to the expectation that either stereoisomer would be active in the assay, with an expectation that one is likely to be more active than the other, based on the stereospecific nature of cellular components. Carrying out the experiment is necessary to determine which stereoisomer will be more active in a given therapy. As is present on the record this rationale is consistent with the court's decision in *In re Adamson and Duffin*, 128 USPQ 233 (CCPA 1960).

Furthermore, even if an unexpected result is considered to be present, based on the fact that a different assay is used, the result is not commensurate in scope with any of the instant claims; only two cancer cell lines (not two genera of cancer types) have been established to have activity with the D-isomer. This is not commensurate in scope with even claim 134, which is limited to the generic cancers of all melanoma or lung cancers.

Applicant argues the facts in *Adamson* are not analogous to the current facts that the claims at issue in *Adamson* were composition claims, not method claims. Even so, the decision is on the same basis as is discussed here, that it would have been obvious to isolate the two stereoisomers, test each one, and find that one would be more active than the other. This finding does not render the composition nonobvious, based on this ruling. Since an assay is conducted in *Adamson*, the facts are also considered applicable to a method, which merely carries out an assay, such as is discussed in

Adamson, and for which there was declaration evidence demonstrating one stereoisomer had better activity than the other, just as in the instant case.

Applicant further argues in *Adamson* there was no prior art teaching away from using the claimed isomer. This has not been established in the instant case either, see discussion above, with respect to this argument. As discussed above, both stereoisomers have demonstrated activity in the Peterson assay; the fact that the D isomer is less potent is insufficient to establish a teaching away.

Applicant argues *Forrest Laboratories v. Ivax Pharmaceuticals, Inc*, 501 F.3d 1263 (Fed. Cir. 2007) the Federal Circuit affirmed that the (+)- enantiomer of citalopram was obvious over the known racemate when it was shown that the therapeutic properties of the (+) enantiomer were unexpected. There is no evidence that there is an unexpected result, except potentially for experiments involving two cell lines, this is evidence not commensurate in scope with any instant claim. Review of *Forrest* indicates there is another significant factor, which is critical in weighing the decision. In *Forrest*, there is evidence that the known method for isolating the stereoisomers did not work when the inventor spent two years attempting to separate out the stereoisomers, and that the method of making (see p. 1104):

In response, Forest argues that any prima facie obviousness based on racemic citalopram was rebutted by the evidence demonstrating the difficulty of separating the enantiomers and the unexpected properties of (+)-citalopram. Forest argues that it was unexpected that all of the therapeutic benefit of citalopram would reside in the (+)-enantiomer, resulting in escitalopram having

twice the potency of racemic citalopram. Forest also argues that the district court was entitled to credit evidence that a person of ordinary skill in the art would not easily have turned to the diol intermediate to attempt resolution of racemic citalopram both because of the uncertainty involved and because Wilen and Jacobus describe compounds less complex than those necessary here to resolve the diol intermediate and then convert the (-)-diol enantiomer to escitalopram. The fact that the method for preparing the stereoisomers was not enabled from merely the statement that the stereoisomers are separable, and the method of making the (+)-enantiomer involved a procedure that wouldn't have been expected to yield the stereoisomer. The fact of difficulty in preparing the claimed stereoisomer is not present in the instant rejection basis; in fact, Peterson specifically points to methods provided in the literature for preparing each of the D and L stereoisomers of 1-methyl tryptophan (see p. 540, lines 7-8). Therefore, *Forrest* is not considered to have the same fact pattern as the instant rejection basis.

The fact pattern of *Adamson* is considered to be identical to or at least much closer to the instant fact pattern. Based on *Adamson*, the rejection is still considered proper.

Conclusion

5. No claim is allowed.
6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571) 272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1628